REVISION OF MONOGRAPH ON CAPSULES

Final text for addition to The International Pharmacopoeia

(July 2012)

DRAFT FOR COMMENT

Should you have any comments on the attached revision, please send these to Dr Herbert Schmidt, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22) 791 4730 or e-mail: schmidt@who.int (with a copy to gaspardm@who.int) by 7 September 2012.

We will now send out our working documents electronically and they will also be placed on the Medicines web site for comment. If you do not already receive our documents please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list.

© World Health Organization 2012

All rights reserved.

This draft is intended for a restricted audience only, i.e. the individuals and organizations having received this draft. The draft may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means outside these individuals and organizations (including the organizations’ concerned staff and member organizations) without the permission of WHO. The draft should not be displayed on any web site.

Please send any request for permission to:
Dr Sabine Kopp, Quality Assurance Programme, Medicines Quality Assurance Programme, Quality & Safety: Medicines, Department of Essential Medicines and Health Products, World Health Organization, CH-1211 Geneva 27, Switzerland. Fax: (41-22) 791 4730; e-mail: kopp@who.int.

The designations employed and the presentation of the material in this draft do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this draft. However, the printed material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This draft does not necessarily represent the decisions or the stated policy of the World Health Organization.
**SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/12.504**

**Revision of monograph on capsules**

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discussion of revision at consultation on specifications for <em>The International Pharmacopoeia</em> and quality control issues</td>
<td>29-31 May 2012</td>
</tr>
<tr>
<td>Draft revision mailed out for comments</td>
<td>July 2012</td>
</tr>
<tr>
<td>Collation of comments</td>
<td>August-September 2012</td>
</tr>
<tr>
<td>Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations for discussion</td>
<td>9-12 October 2012</td>
</tr>
<tr>
<td>Further follow-up action as required</td>
<td></td>
</tr>
</tbody>
</table>
REVISION OF MONOGRAPH ON CAPSULES

Final text for addition to The International Pharmacopoeia

The requirements of this monograph do not necessarily apply to preparations that are intended for use other than by oral administration, such as vaginal or rectal capsules etc. Such preparations may require a special formulation, method of manufacture, or form of presentation, appropriate to their particular use. Starch capsules (often known as cachets) are not included in this monograph.

Definition

Capsules are solid dosage forms with hard or soft shells. They are of various shapes and sizes, and contain a single dose of one or more active ingredients. They are intended for oral administration.

Capsule surfaces may bear symbols or other markings.

Capsule shells are made of gelatin or other substances, the consistency of which may be modified by the addition of substances such as glycerol or sorbitol. The shell should disintegrate in the presence of digestive fluids so that the contents are released. The contents of capsules may be solid, liquid, or of a paste-like consistency. Capsule shells and contents may contain excipients such as diluents, solvents, surface-active substances, opaque fillers, antimicrobial agents, sweeteners, colouring matter authorized by the appropriate national or regional authority, flavouring substances, disintegrating agents, glidants, lubricants, and substances capable of modifying the behaviour of the active ingredient(s) in the gastrointestinal tract. The contents should not cause deterioration of the shell.

When excipients are used, it is necessary to ensure that they do not adversely affect the stability, dissolution rate, bioavailability, safety, or efficacy of the active ingredient(s); there must be no incompatibility between any of the components of the dosage form.

The different categories of capsule include:

- hard capsules;
- soft capsules;
- modified-release capsules [including delayed-release capsules (gastro-resistant/enteric capsules) and sustained-release capsules (extended-/prolonged-release capsules)].

Manufacture

The manufacturing and filling processes for capsules should meet the requirements of good manufacturing practices (GMP).
Very broad guidelines concerning the main critical steps to be followed during production of capsules, indicating those that are the most important, are provided below. Additional guidelines specific for hard or soft capsules are provided in the respective subsections below.

In the manufacture of capsules, measures are taken to:

- ensure that the active ingredient(s) when present in solid state form have appropriate solid-state properties such as particle-size distribution and polymorphic form;
- ensure that mixing with excipients is carried out in a manner that ensures homogeneity;
- minimize the degradation of the active ingredient(s);
- minimize the risk of microbial contamination;
- minimize the risk of cross contamination.

The particle size of the active ingredient(s) may be of primary significance in determining the rate and extent of dissolution and the bioavailability of the drug product, especially for substances of low solubility in aqueous media. The uniformity of the final drug product is affected by the particle size of the active ingredient(s) as well as the excipients.

Throughout manufacturing, certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production.

Packaging is required to be adequate to protect capsules from light when required, and from moisture and damage during transportation.

**Visual inspection**

Unpack and inspect at least 20 capsules. They should be smooth and undamaged. Evidence of physical instability is demonstrated by gross changes in physical appearance, including hardening or softening, cracking, swelling, mottling, or discoloration of the shell.

**Uniformity of mass**

Capsules comply with the test for 5.2 Uniformity of mass for single-dose preparations, unless otherwise specified in the individual monograph.

**Uniformity of content**

Where a requirement for compliance with the test for 5.1 Uniformity of content for single-dose preparations is specified in an individual capsule monograph the test for 5.2 Uniformity of mass for single-dose preparations is not required.
Dissolution/disintegration

Where a choice of test is given ("Either test A or test B may be applied"), follow the instructions in the monograph. Where a requirement for compliance with a dissolution test is specified in the individual monograph, the requirement for disintegration stated in the sections below do not apply.

When justified and authorized the specified disintegration and dissolution media may contain enzymes to overcome failure in the tests caused by cross-linking of the gelatin.

Labelling

Every pharmaceutical preparation must comply with the labelling requirements established under GMP.

The label should include:

(1) the name of the pharmaceutical product;
(2) the name(s) of the active ingredient(s); International Nonproprietary Names (INNs) should be used wherever possible;
(3) the amount of the active ingredient(s) in each capsule and the number of capsules in the container;
(4) the batch (lot) number assigned by the manufacturer;
(5) the expiry date and, when required, the date of manufacture;
(6) any special storage conditions or handling precautions that may be necessary;
(7) directions for use, warnings, and precautions that may be necessary;
(8) the name and address of the manufacturer or the person responsible for placing the product on the market.

Storage

Capsules should be kept in well-closed containers. They should be protected from light when required, and from excessive moisture, or dryness, and should not be subjected to temperatures above 30 °C. Additional special packaging, storage, and transportation recommendations are provided, where necessary, in the individual monograph.
Requirements for specific types of capsules

**Hard capsules**

**Definition**

Hard capsules have shells consisting of two prefabricated cylindrical sections that fit together. One end of each section is rounded and closed, and the other is open. The contents of hard capsules are usually in solid form (powder or granules).

**Manufacture**

Sometimes, the physical characteristics of the mixture of the active ingredient(s) and excipients allow it to be directly filled into the shell, but it may occasionally be necessary to granulate before filling. Normally the granulate needs to be mixed with lubricants and/or disintegrating agents. The use of excessive amounts of lubricants should be avoided since these may deleteriously affect the capsules.

In-process controls during hard capsule production should include the moisture content of the mixture and/or granulate (as well as of the shells), the size of granules, the flow of the final mixture, and the uniformity of mass, capsule size, integrity of the seals, and disintegration or dissolution rate (e.g. for modified-release capsules) of the finished dosage form.

**Disintegration test**

Hard capsules comply with 5.3 Disintegration test for tablets and capsules.

Use water as the immersion fluid unless hydrochloric acid (0.1 mol/l) VS or other medium is specified in the individual monograph. Operate the apparatus for 30 minutes, unless otherwise justified and authorized and examine the state of the capsules.

If capsules float, use a disc as described under 5.3 Disintegration test for suppositories.

**Soft capsules**

**Definition**

Soft capsules have thicker shells than hard capsules, and antimicrobial preservatives are usually added. The shells are of one piece and various shapes. The contents of soft capsules are usually solutions or suspensions of the active ingredient(s) in non-aqueous liquids. Partial migration of the contents into the shell may occur (and vice versa) depending on the nature of the materials used and the product in question.
Manufacture

Soft capsules are usually formed, filled, and sealed in one operation. However, shells for extemporaneous use are sometimes prefabricated. Liquids may be incorporated directly. Solids are usually dissolved or dispersed in a suitable excipient(s) to give a solution, suspension or dispersion of paste-like consistency.

In-process controls during soft capsule production should include the viscosity of the contents, and the uniformity of mass, capsule size, integrity of the seals, and disintegration or dissolution rate (e.g. for modified-release capsules) of the finished dosage form.

Disintegration test

Soft capsules comply with 5.3 Disintegration test for tablets and capsules, using water as the immersion fluid unless hydrochloric acid (0.1 mol/l) VS or other medium is specified in the individual monograph. Add a disc to each tube. Liquid active substances dispensed in soft capsules may attack the disc; in such circumstances and where authorized, the disc may be omitted. Operate the apparatus for 30 minutes and examine the state of the capsules. If the capsules fail to comply because of adherence to the discs, the results are invalid. Repeat the test on a further 6 capsules omitting the discs.

Modified-release capsules

Definition

Modified-release capsules are hard or soft capsules in which the contents or the shell or both contain excipients or are prepared by special procedures such as micro-encapsulation which, separately or together, are designed to modify the rate, place or time of release of the active ingredient(s) in the gastrointestinal tract.

Sustained-release capsules (Extended- or Prolonged-release capsules)

Definition

Sustained-release capsules are designed to slow the rate of release of the active ingredient(s) in the gastrointestinal tract.

All requirements for these specialized dosage forms are given in the individual monographs.
Delayed-release capsules (gastro-resistant/enteric capsules)

Definition

Delayed-release capsules are hard or soft capsules prepared in such a manner that either the shell or the contents resist the action of gastric fluid but release the active ingredient(s) in the presence of intestinal fluid.

Manufacture

The additional statements given under either hard or soft capsules apply, as appropriate to delayed-release capsules.

Disintegration test

Delayed-release capsules with a gastro-resistant shell comply with 5.3 Disintegration test for tablets and capsules, using hydrochloric acid (0.1 mol/l) VS as the immersion fluid. Operate the apparatus without the discs for 2 hours, unless otherwise specified in the individual monograph (but in any case for not less than 1 hour), and examine the state of the capsules. No capsule should show signs of disintegration or rupture permitting the contents to escape. Replace the acid by phosphate buffer solution, pH 6.8, TS with added pancreatin R where specified in the individual monograph. Add a disc to each tube. Operate the apparatus for 60 minutes and examine the state of the capsules. If the capsules fail to comply because of adherence to the discs, the results are invalid. Repeat the test on a further 6 capsules omitting the discs.

For capsules in which the contents, rather than the shell, resist the action of gastric fluid, carry out a suitable dissolution test to demonstrate the appropriate release of the active substance(s).